

Expert Opinion

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Treatment of hypertension in the elderly in 2010 – a brief review

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Importance of the field: Populations, the world over, age. Prevalence of hypertension increases with advancing age. Despite the advances over the past 30 years, there are still unresolved issues regarding antihypertensive therapy in the elderly.

Areas covered in this review: The present review discusses the available evidence supporting treatment of hypertension in the elderly.

What the reader will gain: In the 1980s and 1990s, a number of trials were performed and proved that active treatment of hypertension in individuals above the age of 60 – 65 years, compared with placebo or no treatment, reduces the risk of complications. In the 1990s, the same was proven in patients specifically affected with isolated systolic hypertension, the predominant form of hypertension in the elderly. The subsequent years witnessed the publication of trials that showed that most antihypertensive drugs are capable of substantially reducing risk. Finally, treatment of hypertension in the very elderly was proven to be beneficial.

Take home message: In spite of these advances, we still lack evidence in elderly patients with mild isolated systolic hypertension and are therefore in need of a properly designed, randomized, placebo-controlled trial.

Keywords: clinical trial, elderly, hypertension, treatment

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1. Aging of populations and blood-pressure-associated risk

Populations worldwide, especially those in Western and westernized countries, are undergoing a profound demographic change as they age. As recently shown, 50% of people who were born in recent years in countries such as the UK, USA, France, Denmark or Japan will live to celebrate their hundredth birthday [1]. Population-wise, blood pressure (BP) raises with advancing age, resulting in an age-related increase in the prevalence of hypertension [2,3].

The pathophysiology of hypertension in the elderly differs from that implicated in the disease at younger age. The major factor in the pathogenesis of hypertension in the elderly is the progressive stiffening of large conduit arteries with subsequent increase in pulse-wave velocity, resulting in an increase of systolic (SBP) and a decrease of diastolic (DBP) blood pressure [4,5].

Increased SBP has been associated with increased rates of complications, some of which tend to be closely related to pulse pressure. A 10-mmHg higher SBP has been shown to be associated with a substantial increase of risk of major complications such as all-cause mortality (14%), cardiovascular mortality (12%), fatal and non-fatal cardiovascular events (8%) and stroke (12%) [6]. This risk has been shown to be reversible upon effective antihypertensive treatment.

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Article highlights.

- Hypertension is the most important modifiable cardiovascular risk factor.
- Treatment of hypertension in the elderly in general is beneficial.
- Prevention of cardiovascular complications upon treatment of hypertension is due to blood-pressure lowering rather than specific drug properties.
- We are in need of a randomized, placebo-controlled clinical trial to answer the question whether treatment of mild uncomplicated isolated systolic hypertension in the elderly is beneficial.

This box summarizes key points contained in the article.

2. Trials in elderly patients with systolic-diastolic hypertension

Over the past three decades a number of trials have addressed the issue of whether treatment of hypertension in the elderly would be beneficial. The early trials included patients with systolic and/or diastolic hypertension, and treatment decisions were based primarily on DBP.

The Australian Therapeutic Trial in Mild Hypertension (ATTMH) included 582 patients aged ≥ 60 (mean 64) years. The patients were free from cardiovascular complications and their DBP at baseline had to range from 95 to 109 mmHg (mean blood pressure at baseline 167/101 mmHg). Patients were randomized to receive active treatment based on chlorothiazide 500 mg, with possibility of doubling the dose, addition of methyldopa (250 – 2000 mg), propranolol (40 – 320 mg) or pindolol (5 – 30 mg), and clonidine (150 – 900 mg) or hydralazine (10 – 200 mg), or to matching placebos. After 3.9 years of follow-up (median), the composite end point of all-cause mortality and all cardiovascular and renal complications was reduced ($p < 0.025$) in the active treatment group by 39% [7].

The European Working Party on High Blood Pressure in the Elderly (EWPHE) trial included 840 patients aged 60 (mean 72) years and more. The patients' blood pressure at entry had to be in the range of 160 – 239 mmHg SBP and 90 – 119 mmHg DBP (mean blood pressure at baseline 183/101 mmHg). Patients were randomized to receive either active treatment based on hydrochlorothiazide (25 mg)/triamterene (50 mg), with add-on methyldopa (250 – 2000 mg) or matching placebos. The actively treated patients, after mean follow-up of 4.6 years, experienced 27% ($p = 0.037$) fewer cardiovascular deaths but not deaths of any cause (9% reduction, $p = 0.41$) [8].

The Hypertension in Elderly Patients in Primary Care (HEP) trial included 884 patients aged 60 – 79 (mean 69) years with an SBP of ≥ 170 mmHg or DBP of ≥ 105 mmHg (mean blood pressure at baseline 196/99 mmHg). Patients were randomly assigned to receive

active treatment based on atenolol (100 mg), bendrofluasid (5 mg), a combination of the two with add-on methyldopa (500 mg) or no treatment. After mean follow-up of 4.4 years, there were 42% fewer strokes ($p < 0.03$) in the actively treated group, the benefit that was mainly driven by a 70% reduction of fatal stroke ($p < 0.025$). Neither the incidence of myocardial infarction nor total mortality differed significantly between the groups [9].

The Swedish Trial in Old Patients with Hypertension (STOP1) included 1627 individuals aged between 70 and 84 (mean 76) years. To be included, the patients' SBP had to be between 180 and 230 mmHg with a DBP of ≥ 90 mmHg; or DBP had to be between 105 and 120 mmHg irrespective of SBP (mean blood pressure at baseline 195/102 mmHg). Patients were randomly assigned to receive either active treatment, based on atenolol (50 mg), metoprolol (100 mg), pindolol (5 mg) or hydrochlorothiazide (25 mg)/amiloride (2.5 mg), or matching placebos. The actively treated patients experienced 40% ($p = 0.0031$) fewer strokes, myocardial infarctions and other cardiovascular deaths combined, with 47% ($p = 0.0081$) fewer strokes, 76% fewer fatal strokes and 70% fewer cardiovascular deaths. Total mortality was reduced by 43% ($p = 0.0079$) [10].

In the Medical Research Council trial of treatment of hypertension in older adults (MRC2), 4396 patients aged between 65 and 74 (mean 70) years, whose SBP was 160 – 209 mmHg and DBP < 115 mmHg (mean blood pressure at baseline 185/91 mmHg), were randomized to active treatment based on a diuretic (hydrochlorothiazide 25 – 50 mg/amiloride 2.5 – 5 mg) or a beta-blocker (atenolol 50 – 100 mg) with add-on nifedipine (20 mg) and two matching placebo groups. The combined analysis showed that actively treated patients, after 5.8 years of follow-up, had 25% ($p = 0.04$) fewer strokes and 17% ($p = 0.03$) fewer cardiovascular complications.

Subgroup analysis revealed the effect to be driven by the group treated with diuretic and absent in the group that received atenolol; it was observed mostly in nonsmoking patients (Table 1) [11].

3. Trials in elderly patients with isolated systolic hypertension

Three large-scale trials addressed the issue of treatment of isolated systolic hypertension (ISH) in the elderly. The Systolic Hypertension in the Elderly Program (SHEP) included 4763 patients aged ≥ 60 (mean 72) years with SBP of ≥ 160 mmHg and DBP of < 90 mmHg (mean blood pressure at baseline 170/77 mmHg). Over the mean follow-up of 4.5 years, the chlorthalidone (12.5 – 25 mg, with add-on atenolol 25 mg and reserpine 0.05 mg)-based therapy, compared with placebo, reduced the incidence of stroke by 36% ($p < 0.0003$) and fatal and nonfatal cardiovascular events by 32% (95% CI, 20 – 44%); however, total mortality did not differ between the randomization groups [12].

Table 1. Summary characteristics of trials.

Trial	Ref.	Design	No. of pts	Drug tested	Drug reference	Primary end point	Age (years)	SBP/DBP (mmHg)	BP gradient (mmHg)*	FU
ATTMH	[7]	DB	582	Ctz/Mtd/Prp(Pin)	Pcb	TM + CVM + S + MI + CAD + CHF + AoD + EPAT + REN + RET	64	167/101	.../6.7	3.9
EWPHE	[8]	DB	840	Hctz + Tri/Mtd	Pcb	TM + CVM + S [‡] + CHF + RET + HT + DRG + LVH + REN	72	183/101	20.0/5.0	4.7
HEP	[9]	O	880	At/Bfa/Mtd	...	TM + MI + S	69	196/99	18.0/11.0	4.4
STOP1	[10]	DB	1627	(At) (HCTza)	Pcb	CVM + S + MI	76	195/102	19.5/8.1	2.1
MRC2	[11]	SB	4396	(Met)(Pin) (Hctza)(At)/(At) (Hctza)/Nit	Pcb	TM + CVM + S + MI	70	185/91	17/6 [§]	5.8
SHEP	[12]	DB	4736	Cld/At/(Res)	Pcb	FS + S	72	170/77	11.5/4.1	4.4
Syst-Eur	[13]	DB	4695	Nit/Ena/Hctz	Pcb	FS + S	70	174/85	10.2/3.5	2.0
Syst-China	[15]	SB	2394	Nit/Cap/ Hctz	Pcb	FS + S	67	170/86	6.9/2.3	3.0
LIFE-ISH	[18]	DB	1326	Los/Hctz	At/Hctz	CVM + MI + S	70	174/83	0/0	4.7
ANBP2	[16]	O	6083	Hctz	Ena	CVM + FS + S + MI + HF	72	168/79	0/0	4.1
SCOPE	[17]	DB	4964	Can/Hctz	Pcb	CVM + S + MI	76	166/90	3.2/1.6	3.7
SHELL	[19]	O	1882	Lcdp	Cld	CVM + FS + S + MI + HF	72	178/87	1.6/0.2	2.6
INSIGHT-ISH	[20]	DB	1498	Nif/At/(Ena)	Hctza/At/(Ena)	CVM + FS + MI + HF	66	173/88	1.0/0.0	3.0
HYVET	[25]	DB	3845	Ind/Per	Pcb	FS + S	84	173/91	15.0/6.1	2.0

*Baseline-adjusted difference in the on-treatment blood pressure (reference minus tested). Add-on medications appear after/. Features appearing in parentheses are alternative options.

[†]Nonfatal cerebral haemorrhage.

[‡]Based on visual inspection of a figure from original report.

AoD: Aortic aneurysm dissection; At: Atenolol; Bfa: Bendrofluzide; CAD: Coronary artery disease other than MI; Can: Candesartan; Cap: Captopril; CHF: Congestive heart failure; CLTD: Chorothalidone; CTZ: Chlorothiazide; CVM: Cardiovascular mortality; DB: Double-blind; DRG: Need to introduce betablocker/calcium channel blocker/diuretic; Ena: Enalapril; EPAT: Hypertensive encephalopathy; FS: Fatal stroke; HCTZ: Hydrochlorothiazide; Hctza: Hydrochlorothiazide + amiloride; HF: Hospitalized heart failure; HT: Severe increase in BP; Ind: Inapamide; Lcdp: Lacidipine; Los: Losartan; LVH: Severe left ventricular hypertrophy or dilatation; MI: Nonfatal myocardial infarction; Mtd: Methyldopa; Nif: Nifedipine; Nit: Nitrendipine; O: Open; Pcb: Placebo; Per: Perindopril; Pin: Pindolol; Prp: Propranolol; REN: Renal failure; Res: Reserpine; RET: Retinal haemorrhage/exudate/papilloedema; S: Single-blind; SB: Nonfatal stroke; S: Nonfatal stroke; S: Single-blind; TM: All-cause mortality; Tri: Triamterene

The Systolic Hypertension in Europe (Syst-Eur) trial included 4695 elderly patients with ISH (mean age 70 years; mean blood pressure at baseline 174/86 mmHg). Active treatment based on nitrendipine (10 – 40 mg) with add-on enalapril (5 – 20 mg) and hydrochlorothiazide (12.5 – 25 mg), compared with matching placebos, reduced the incidence of fatal and nonfatal stroke by 42% ($p < 0.003$), and fatal and nonfatal cardiovascular events combined by 31% ($p < 0.001$), with a borderline trend towards a reduction in cardiovascular mortality by 27% ($p = 0.07$) [13]. The effect of treatment was especially pronounced in patients with diabetes mellitus. This has been the only trial so far to show clear-cut, 50% ($p = 0.05$) reduction in the incidence of dementia associated with active treatment of hypertension [14].

Finally, the Systolic Hypertension in China (Syst-China) trial confirmed the findings of both SHEP and Syst-Eur in 2394 Chinese elderly patients with ISH [15].

In 2000, Staessen *et al.* carried out a quantitative overview of ISH in the elderly based on large randomized trials that emerged in the 1980s and 1990s [6]. This meta-analysis incorporated the SHEP, Syst-Eur and the Syst-China trials, involving exclusively elderly patients with ISH (SBP 160 mmHg or higher), and also the EWPHE, HEP, STOP1 and MRC1 trials, which included subgroups of elderly patients with ISH, and the MRC2 trial, which involved older adults. This paper, based thus on eight trials (15,693 patients; mean age ranged 62 – 76 years), showed that active treatment in elderly patients with ISH compared with placebo or no treatment reduced total mortality by 13% ($p = 0.02$), cardiovascular mortality by 18% ($p = 0.01$), stroke events by 30% ($p < 0.0001$) and coronary events by 23% ($p = 0.002$), and all cardiovascular events by 25% ($p < 0.0001$) [6]. Therefore, these landmark clinical trials provide convincing support for the routine treatment of ISH in elderly patients (Table 1).

4. Trials testing newer drug classes in elderly patients

Following the encouraging findings of the early trials in treating systolic hypertension in older subjects, many new trials have focused on elucidating the effects of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs) and other blood-pressure-lowering drugs on mortality and major cardiovascular morbidity (Table 1) [16-20].

The Second Australian National Blood Pressure Study (ANBP2) included 6083 patients aged 65 – 84 years with mild to moderate hypertension (mean age 71.9 years; mean blood pressure 168/91 mmHg) [16]. Patients were randomized to receive active treatment based on enalapril or hydrochlorothiazide, with possible addition of beta-blockers or CCBs. After median follow-up of 4.1 years, patients treated with the enalapril-based regimen had an 11% lower rate of primary composite end point (all-cause mortality and cardiovascular

events combined). However, the effect was driven by a 17% between-group difference observed in men, but not women [16].

The Study of Cognition and Prognosis in the Elderly (SCOPE), a prospective, double-blind, randomized, parallel-group study, examined the effects of the ARB candesartan on cardiovascular events, stroke and cognition in 4964 elderly patients with mild hypertension (mean age 76.4 years; mean blood pressure 166.3/90.3 mmHg) [17]. After a mean follow-up of 3.7 years, the ARB-based treatment reduced nonfatal stroke by 27.8% and fatal and nonfatal stroke by 23.6%. There were no significant differences in myocardial infarction and cardiovascular mortality, and cognitive function was well maintained in both the active treatment and placebo groups.

The Losartan Intervention for Endpoint Reduction (LIFE) trial was a randomized, double-blind study that examined the effects of the ARB losartan on cardiovascular mortality, stroke and myocardial infarction [18]. In a subgroup analysis of the trial, the LIFE-ISH, 1326 elderly patients with isolated hypertension (mean age 70.3 years; mean blood pressure 174/83 mmHg) and left ventricular hypertrophy received once-daily losartan (50 – 100 mg) or atenolol (50 – 100 mg) (with hydrochlorothiazide 12.5 – 25 mg, as the second agent in both arms) for a mean of 4.7 years. The composite end point of cardiovascular death, stroke or myocardial infarction was reduced by 25% ($p = 0.02$) with losartan compared with atenolol.

The Systolic Hypertension in the Elderly Long-term Lacidipine (SHELL) study compared the effect of lacidipine (4 – 6 mg) and chlorthalidone (12.5 – 25 mg) in 1882 elderly patients with ISH (age ≥ 60 years; mean blood pressure 178/87 mmHg) followed for 32 months [19]. Both drugs markedly reduced SBP and the overall incidence of the primary end point, a composite of cardiovascular and cerebrovascular events, was 9.3% in both groups. The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study included 6321 patients aged 55 – 80 years with hypertension and at least one additional cardiovascular risk factor. Although not a selective ISH trial, INSIGHT contained a subgroup of 1498 patients with ISH (mean blood pressure 173/88 mmHg) that was analyzed separately (INSIGHT-ISH) [20]. In the subgroup analysis, the CCB nifedipine GITS (30 – 60 mg) was compared with the diuretic combination hydrochlorothiazide/amiloride (25/2.5 – 50/5 mg), with add-on enalapril (5 – 10 mg), and it evaluated a composite end point of death due to cardiovascular and cerebrovascular causes and nonfatal stroke, myocardial infarction and heart failure. Both treatments had similar effects on blood-pressure lowering and on the primary outcome (6.0% with nifedipine, 6.6% with hydrochlorothiazide/amiloride).

Several short-term studies compared the blood-pressure-lowering effects and safety of ARBs and CCBs in elderly patients with ISH. Valsartan and Amlodipine for the

Treatment of Isolated Systolic Hypertension in the Elderly (Val-Syst), a 24-week randomized, double-blind study, compared the risk/benefit profiles of the ARB valsartan with the CCB amlodipine in 421 elderly (aged 60 – 80 years) patients with ISH [21]. The results showed that valsartan, given alone or in combination with hydrochlorothiazide, showed similar efficacy but better tolerability than amlodipine-based treatment. Another randomized, double-blind, placebo-controlled, 12-week study compared the effects of the diuretic indapamide with the ARB candesartan and the CCB amlodipine in 1758 patients (aged 40 – 80 years) with hypertension [22]. In a subgroup of patients with ISH ($n = 388$, mean age 64 years), the three treatments significantly reduced SBP; though indapamide did not change DBP and, thus, reduced pulse pressure significantly.

The findings from these recent clinical trials demonstrate that blockade of the renin-angiotensin system at various points in the cascade are effective blood-pressure-lowering medications. Studies comparing ARBs with other regimens showed a lower incidence of stroke, but not of other cardiovascular outcomes, with renin-angiotensin-directed regimens, and equivalence of non-renin-angiotensin treatments in reducing events (CCBs, diuretics) based on degree of blood pressure lowering.

Encouraging results have recently been reported with aliskiren, the first representative of a new class of nonpeptide, orally active renin inhibitors. The AGELESS trial (Aliskiren for Geriatric Lowering of Systolic Hypertension), compared the efficacy of aliskiren with ramipril in systolic hypertension (SBP ≥ 140 mmHg) in patients aged ≥ 65 years and demonstrated that aliskiren had superior potency for lowering SBP and DBP, provided greater attainment of blood pressure goal and required less add-on therapy compared with ramipril in elderly patients with systolic hypertension [23]. This was a 36-week, randomized, double-blind, parallel-group, active-controlled, optional-titration study of 901 elderly patients (aliskiren, $n = 457$; ramipril, $n = 444$). Decreases from baseline mean sitting SBP and mean sitting DBP with aliskiren monotherapy (-14.0 and -5.1 mmHg, respectively) were non-inferior ($p < 0.001$ for both values) and superior to ramipril monotherapy (-11.6, -3.6 mmHg; $p = 0.02$, $p < 0.01$, respectively). However, data on long-term mortality and morbidity are needed.

5. Treatment of hypertension in the very elderly

Until recently, the best available data on hypertensive people aged > 80 years came from the Individual Data Analysis of Antihypertensive Drug Intervention Trials (INDANA) group. This database included 1670 patients above 80 years of age who were randomized in seven clinical trials that compared active drug therapy versus placebo or no treatment [24]. Octogenarians (mean age 83 years) comprised only 13% of the overall population in these trials. In this meta-analysis, active

drug therapy significantly reduced fatal and nonfatal strokes by 34% and major cardiovascular events by 22%; but mortality and cardiovascular death rates were higher, by 6 and 1%, respectively – though these increases were not statistically significant. However, the Hypertension in the Very Elderly Trial (HYVET; 3845 patients, aged ≥ 80 years) has proved that it is not too late to start antihypertensive therapy in older people [25]. In short, the active treatment based on indapamide sustained-release (1.5 mg) with add-on perindopril (2 – 4 mg) produced significant reductions in the risk of death from any cause by 21% ($p = 0.02$), fatal stroke by 39% ($p = 0.05$), and incident heart failure by 64% ($p < 0.001$), with borderline significant reductions in incidence of fatal and nonfatal stroke by 30% ($p = 0.06$) and cardiovascular mortality by 23% ($p = 0.06$). This publication expands the upper limit of the age spectrum for which there is evidence from clinical trials of a treatment benefit (Table 1) [24,25].

6. Message reinforced

In a very recent meta-analysis, Musini *et al.* identified 15 trials of at least 1 year's duration (24,055 patients) of hypertension in the elderly (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) including the HYVET trial [26]. These trials mostly evaluated first-line thiazide diuretic therapy for a mean duration of treatment of 4.5 years versus placebo or no treatment. The authors showed that treatment reduced total mortality (response rate (RR) = 0.90, confidence interval (CI) 0.84 – 0.97) and total cardiovascular morbidity and mortality (RR = 0.72, CI 0.68 – 0.77) owing to reduction in both cerebrovascular as well as coronary heart disease mortality and morbidity. They confirmed similar results in the three trials restricted to persons with ISH (RR = 0.68, CI 0.61 – 0.75). In very elderly patients (≥ 80 years old), treatment reduced total cardiovascular mortality and morbidity (RR = 0.75, CI 0.65 – 0.87) only, owing to cerebrovascular mortality and morbidity (RR = 0.66, CI 0.52 – 0.83), whereas no reduction in total mortality was observed (RR = 0.98, CI 0.87 – 1.10). The authors have also drawn attention to the withdrawals due to adverse effects that were associated with treatment (RR = 1.71, CI 1.45 – 2.00). However, the patients included in HYVET were relatively healthy and a low proportion had experienced cardiovascular complications before inclusion [26].

7. Choice of regimen

Most elderly patients with hypertension will need more than one drug for blood pressure control. Combining antihypertensive drugs with complementary mechanisms of action has many benefits, including greater antihypertensive efficacy and lower rates of dose-related adverse events, because lower doses of the individual components than would be used in monotherapy can be administered. The use of fixed-dose combination pills may also lower overall cost and improve

Hypertension in the elderly

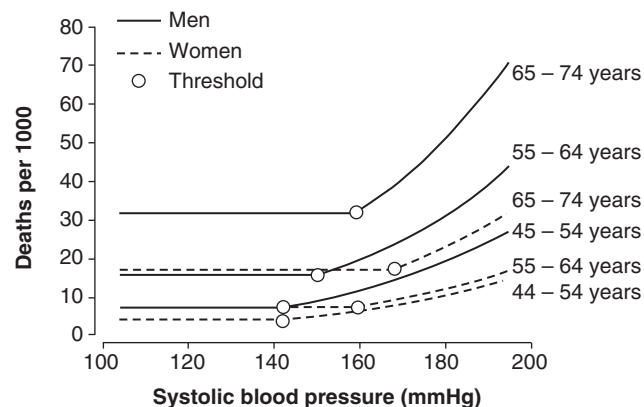


Figure 1. Relation between systolic blood pressure and risk of death.

The cut-off is age- and sex-dependent. Reanalysis of data from Framingham Heart Study. Reproduced with permission from [35].

medication adherence in elderly individuals with hypertension. The guidelines encourage the use of diuretics, both as first-line treatment and in combination with other drugs. The choice of a second agent or a first-line drug, if a patient cannot take thiazide-type diuretics, depends on specific compelling indications. In elderly patients with moderate ISH, a diuretic or long-acting dihydropyridine CCB is recommended for initiation of therapy, largely based on the results from SHEP, Syst-Eur and Syst-China [12,13,15]. On the other hand, data from the Avoiding Cardiovascular Complications in Patients Living with Isolated Systolic Hypertension (ACCOMPLISH) trial, seem to indicate that the ACE inhibitor plus CCB combination is better than ACE-inhibitor plus diuretic. However, the ACCOMPLISH trial has been criticized because it used low-dose hydrochlorothiazide in the ACE inhibitor plus diuretic arm [27]. Chlorthalidone, used in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial [28] and other National Heart, Lung, and Blood Institute-sponsored trials, has a longer duration of action than hydrochlorothiazide, and it is more effective in lowering blood pressure. In the Multiple Risk Factor Intervention Trial (MRFIT), hydrochlorothiazide was associated with an unfavorable trend in mortality, and hence the protocol was amended after about 5 years of randomization, and chlorthalidone was used in place of hydrochlorothiazide, which seems to have caused a more favorable mortality trend [29]. The CCBs are metabolically neutral as they do not induce the metabolic side effects common on thiazide diuretics. In a meta-analysis in which 9 of 13 trials involved hypertensives older than 60 years, CCBs have been found to decrease the risk of stroke more effectively than other antihypertensive agents [30]. A meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration analyzed results of 31 trials that compared an ACE inhibitor or a

CCB versus placebo or compared different antihypertensive drug regimens (ACE inhibitor vs diuretic or beta-blocker, CCB vs diuretic or beta-blocker, and ACE inhibitor vs CCB) [31]. The study outcomes included total major cardiovascular events (fatal and nonfatal stroke, nonfatal myocardial infarction or death from coronary heart disease, or heart failure) and compared the effects on the primary outcome between the < 65-year-old and \geq 65-year-old age groups. The analysis did not show substantial age-related difference in the effect of treatment, which included diuretics or beta-blockers, CCBs and ACE inhibitors; hence, the beneficial effects were attributed primarily to blood pressure reduction achieved rather than the choice of drug [31].

8. Compliance

The treatment of hypertension in the elderly presents many challenges. Elderly persons with hypertension usually take several medications for a variety of concomitant conditions, mostly chronic, and this makes them more likely to mismanage their antihypertensive medications. Many medications frequently taken by elderly patients, such as NSAIDs, interfere with the actions of antihypertensive medications. Additionally, orthostatic hypotension, a condition common in the elderly, may be aggravated by antihypertensive treatment [32]. High blood pressure also exacerbates aging-related cognitive decline and may predispose to the development of dementia in the elderly [33]. The higher incidence of cognitive and memory impairment in the elderly necessitates the use of simple antihypertensive regimens to improve medication adherence and blood pressure control.

9. Future directions and expert opinion

Treatment of hypertension in elderly patients is, largely, beneficial. It reduces health burden to the society while decreasing the suffering of affected individuals and their families. However, the evidence we have at present does not apply equally to all our elderly hypertensive patients. It is widely accepted that the relationship between level of blood pressure and cardiovascular risk is linear and universal across age groups [34]. On the other hand, some data point to the possibility that in older individuals the SBP cut-off value for increase in cardiovascular risk is 160 mmHg rather than 140 mmHg (Figure 1) [35]. Similarly, no trial in elderly hypertensives has included patients with mild ISH with SBP in the range of 140 – 150 mmHg, marking a lack of trial evidence for the guideline recommendation to lower SBP in such individuals to < 140 mmHg – an issue recently appreciated in the guideline reappraisal document [36,37] (Figure 2). The only trial so far that has tested the hypothesis that more stringent (goal SBP < 140 mmHg) blood pressure control in elderly patients would be beneficial, the JATOS (Japanese trial to assess optimal systolic blood pressure in

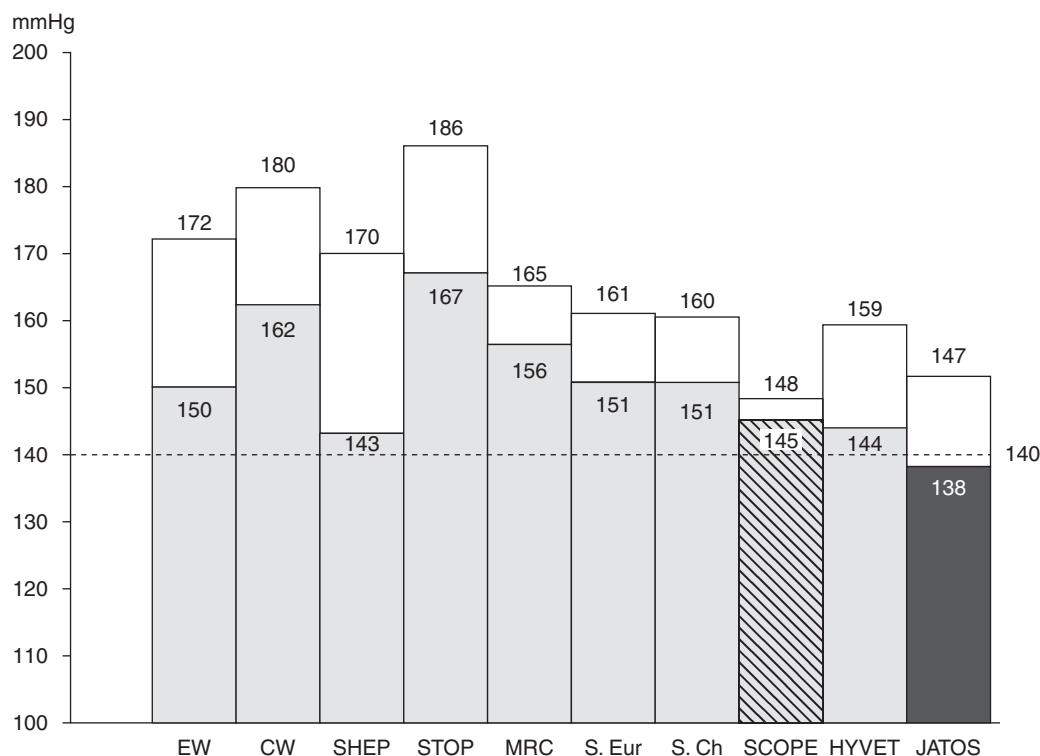


Figure 2. Goal blood pressure and overall result of a trial.

EW: EWPHE (European Working Party on High Blood Pressure in the Elderly trial); CW: HEP (Hypertension in Elderly Patients in Primary Care trial); MRC: MRC2 (Medical Research Council trial of treatment of hypertension in older adults); S. Eur: Syst-Eur (Systolic Hypertension in Europe trial); S. Ch: Syst-China (Systolic Hypertension in China trial); SCOPE: Study of Cognition and Prognosis in the Elderly; SHEP: Systolic Hypertension in the Elderly Program; STOP: Swedish Trial in Old Patients with Hypertension; HYVET: Hypertension in the Very Elderly Trial; JATOS: Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients. Benefit was observed in all trials except SCOPE (partial benefit – hatched bar) and JATOS (no benefit – dark grey bar). Reproduced with permission from [37].

elderly hypertensive patients) trial, yielded negative results [38]; and some data point to the possibility of a J-shaped relation between blood pressure and cardiovascular complications, especially in older patients with clinically more advanced atherosclerosis or with diabetes mellitus [39]. Both issues can and should be resolved to avoid unnecessary treatment or to avoid unnecessary cerebrovascular and cardiovascular morbidity and mortality. We clearly need a placebo-controlled clinical trial to guide us in what seems

to be one of the last *terrae incognitae* of antihypertensive therapy in the elderly.

Declaration of interest

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